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(54) Title: INHIBITORS OF SERINE PROTEASES, PARTICULARLY HEPATITIS C VIRUS NS3 PROTEASE

(57) Abstract

The present invention relates to compounds, methods and pharmaceutical compositions for inhibiting proteases, particularly serine proteases, and more particularly HCV NS3 proteases. The compounds, and the compositions and methods that utilize them, can be used, either alone or in combination to inhibit viruses, particularly HCV virus.

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INHIBITORS OF SERINE PROTEASES, PARTICULARLY HEPATITIS C VIRUS NS3 PROTEASE

TECHNICAL FIELD OF THE INVENTION

The present invention relates to a novel class of compounds that are useful as protease inhibitors, particularly as serine protease inhibitors, and more particularly as hepatitis C NS3 protease inhibitors. As such, they act by interfering with the life cycle of the hepatitis C virus and are also useful as antiviral agents.

This invention also relates to pharmaceutical compositions comprising these compounds. The compounds and pharmaceutical compositions of this invention are particularly well suited for inhibiting HCV NS3 protease activity and consequently, may be advantageously used as therapeutic agents against the hepatitis C virus and other viruses that are dependent upon a serine protease for proliferation. This invention also relates to methods for inhibiting the activity of proteases, including hepatitis C virus NS3 protease and other serine proteases, using the compounds of this invention and related compounds.

BACKGROUND OF THE INVENTION

Infection by hepatitis C virus ("HCV") is a compelling human medical problem. HCV is recognized as

the causative agent for most cases of non-A, non-B hepatitis, with an estimated human seroprevalence of 1% globally [Purcell, R.H., "Hepatitis C virus: Historical perspective and current concepts" FEMS Microbiology Reviews 14, pp. 181-192 (1994); Van der Poel, C.L., "Hepatitis C Virus. Epidemiology, Transmission and Prevention in Hepatitis C Virus. Current Studies in Hematology and Blood Transfusion, H.W. Reesink, Ed., (Basel: Karger), pp. 137-163 (1994)]. Four million individuals may be infected in the United States alone [Alter, M.J. and Mast, E.E., "The Epidemiology of Viral Hepatitis in the United States, Gastroenterol. Clin. North Am. 23, pp. 437-455 (1994)].

Upon first exposure to HCV only about 20% of infected individuals develop acute clinical hepatitis while others appear to resolve the infection spontaneously. In most instances, however, the virus establishes a chronic infection that persists for decades [Iwarson, S. "The Natural Course of Chronic Hepatitis" FEMS Microbiology Reviews 14, pp. 201-204 (1994)]. This usually results in recurrent and progressively worsening liver inflammation, which often leads to more severe disease states such as cirrhosis and hepatocellular carcinoma [Kew, M.C., "Hepatitis C and Hepatocellular Carcinoma", FEMS Microbiology Reviews, 14, pp. 211-220 (1994); Saito, I., et al. "Hepatitis C Virus Infection is Associated with the Development of Hepatocellular Carcinoma" Proc. Natl. Acad. Sci. USA 87, pp. 6547-6549 (1990)]. Unfortunately, there are no broadly effective treatments for the debilitating progression of chronic HCV.

The HCV genome encodes a polyprotein of 3010-3033 amino acids [Choo, Q.-L., et al. "Genetic Organization and Diversity of the Hepatitis C Virus", Proc. Natl. Acad. Sci. USA, 88, pp. 2451-2455 (1991); Kato, N. et al., Molecular Cloning of the Human Hepatitis C Virus Genome From Japanese Patients with Non-A, Non-B Hepatitis", Proc. Natl. Acad. Sci. USA, 87, pp. 9524-9528 (1990); Takamizawa, A. et al., "Structure and Organization of the Hepatitis C Virus Genome Isolated From Human Carriers", J. Virol., 65, pp. 1105-1113 (1991)]. The HCV nonstructural (NS) proteins are presumed to provide the essential catalytic machinery for viral replication. The NS proteins are derived by proteolytic cleavage of the polyprotein [Bartenschlager, R. et al., "Nonstructural Protein 3 of the Hepatitis C Virus Encodes a Serine-Type Proteinase Required for Cleavage at the NS3/4 and NS4/5 Junctions", J. Virol., 67, pp. 3835-3844 (1993); Grakoui, A. et al. "Characterization of the Hepatitis C Virus-Encoded Serine Proteinase: Determination of Proteinase-Dependent Polyprotein Cleavage Sites", J. Virol., 67, pp. 2832-2843 (1993); Grakoui, A. et al., Expression and Identification of Hepatitis C Virus Polyprotein Cleavage Products", J. Virol., 67, pp. 1385-1395 (1993); Tomei, L. et al., "NS3 is a serine protease required for processing of hepatitis C virus polyprotein", J. Virol., 67, pp. 4017-4026 (1993)].

The HCV NS protein 3 (NS3) contains a serine protease activity that helps process the majority of the viral enzymes, and is thus considered essential for viral replication and infectivity. It is known that mutations

in the yellow fever virus NS3 protease decreases viral infectivity [Chambers, T.J. et. al., "Evidence that the N-terminal Domain of Nonstructural Protein NS3 From Yellow Fever Virus is a Serine Protease Responsible for Site-Specific Cleavages in the Viral Polyprotein", Proc. Natl. Acad. Sci. USA, 87, pp. 8898-8902 (1990)]. The first 181 amino acids of NS3 (residues 1027-1207 of the viral polyprotein) have been shown to contain the serine protease domain of NS3 that processes all four downstream sites of the HCV polyprotein [C. Lin et al., "Hepatitis C Virus NS3 Serine Proteinase: *Trans*-Cleavage Requirements and Processing Kinetics", J. Virol., 68, pp. 8147-8157 (1994)].

The HCV NS3 serine protease and its associated cofactor, NS4A, helps process all of the viral enzymes, and is thus considered essential for viral replication. This processing appears to be analogous to that carried out by the human immunodeficiency virus aspartyl protease, which is also involved in viral enzyme processing HIV protease inhibitors, which inhibit viral protein processing are potent antiviral agents in man, indicating that interrupting this stage of the viral life cycle results in therapeutically active agents. Consequently it is an attractive target for drug discovery. Unfortunately, there are no serine protease inhibitors available currently as anti-HCV agents.

Furthermore, the current understanding of HCV has not led to any other satisfactory anti-HCV agents or treatments. The only established therapy for HCV disease is interferon treatment. However, interferons have significant side effects (Janssen et al., 1994; Renault

and Hoofnagle, 1989) [Janssen, H. L. A., et al. "Suicide Associated with Alfa-Interferon Therapy for Chronic Viral Hepatitis" J. Hepatol., 21, pp. 241-243 (1994)]; Renault, P.F. and Hoofnagle, J.H., "Side effects of alpha interferon. Seminars in Liver Disease 9, 273-277. (1989)] and induce long term remission in only a fraction (~ 25%) of cases [Weiland, O. "Interferon Therapy in Chronic Hepatitis C Virus Infection", FEMS Microbiol. Rev., 14, PP. 279-288 (1994)]. Moreover, the prospects for effective anti-HCV vaccines remain uncertain.

Thus, there is a need for more effective anti-HCV therapies. Such inhibitors would have therapeutic potential as protease inhibitors, particularly as serine protease inhibitors, and more particularly as HCV NS3 protease inhibitors. Specifically, such compounds may be useful as antiviral agents, particularly as anti-HCV agents.

SUMMARY OF THE INVENTION

The present invention provides compounds, and pharmaceutically acceptable derivatives thereof, that are useful as protease inhibitors, particularly as serine protease inhibitors, and more particularly as HCV NS3 protease inhibitors. These compounds can be used alone or in combination with immunomodulatory agents, such as α-, β- or γ-interferons; other antiviral agents such as ribavirin and amantadine; other inhibitors of hepatitic C protease; inhibitors of other targets in the HCV life cycle including the helicase, polymerase,

metalloprotease, or internal ribosome entry; or combinations thereof.

The present invention also provides methods for inhibiting proteases, particularly serine proteases, and more particularly HCV NS3 protease.

The present invention also provides pharmaceutical compositions comprising the compounds of this invention, as well as multi-component compositions comprising additional immunomodulatory agents, such as α-, β- or γ-interferons; other antiviral agents such as ribavirin and amantadine; other inhibitors of hepatitic C protease; inhibitors of other targets in the HCV life cycle including the helicase polymerase metalloprotease or internal ribosome entry; or combinations thereof. The invention also provides methods of using the compounds of this invention, as well as other related compounds, for the inhibition of HCV.

DETAILED DESCRIPTION OF THE INVENTION

In order that the invention herein described may be more fully understood, the following detailed description is set forth. In the description, the following abbreviations are used:

Designation	Reagent or Fragment
Abu	aminobutyric acid
Ac	acetyl
AcOH	acetic acid
Bn	benzyl
Boc	tert-butyloxycarbonyl
Bz	benzoyl

Cbz	carbobenzyloxy
CDI	carbonyldiimidazole
DCE	1,2-dichloroethane
DCM	dichloromethane
DIEA	diisopropylethylamine
DMA	dimethylacetamide
DMAP	dimethylaminopyridine
DMF	dimethylformamide
DPPA	diphenylphosphorylazide
DMSO	dimethylsulfoxide
Et	ethyl
EtOAc	ethyl acetate
FMOC	9-fluorenylmethoxycarbonyl
HbtU	O-benzotriazolyl-N,N,N',N'-tetramethyluronium hexafluorophosphate
HOBt	N-hydroxybenzotriazole
HPLC	high performance liquid chromatography
Me	methyl
MS	mass spectrometry
NMP	N-methyl pyrrolidinone
ND	not determined
Pip	piperidine
Prz	piperazine
PyBrop	bromo-tris-pyrrolidinophosphonium hexafluorophosphate
Pyr	pyridine
THF	tetrahydrofuran
TFA	trifluoroacetic acid
TFE	trifluoroethanol

Tol toluene

The following terms are used herein:

Unless expressly stated to the contrary, the terms "-SO_2-" and "-$S(O)_2$-" as used herein refer to a sulfone or sulfone derivative (i.e., both appended groups linked to the S), and not a sulfinate ester.

The term "substituted" refers to the replacement of one or more hydrogen radicals in a given structure with a radical selected from a specified group. When more than one hydrogen radical may be replaced with a substituent selected from the same specified group, the substituents may be either the same or different at every position.

As used herein, the term "amino" refers to a trivalent nitrogen which may be primary or which may be substituted with 1-2 alkyl groups.

The term "alkyl" or "alkane", alone or in combination with any other term, refers to a straight-chain or branched-chain saturated aliphatic hydrocarbon radical containing the specified number of carbon atoms, or where no number is specified, preferably from 1-10 and more preferably from 1-5 carbon atoms. Examples of alkyl radicals include, but are not limited to, methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, n-hexyl and the like.

The term "alkenyl" or "alkene", alone or in combination with any other term, refers to a straight-chain or branched-chain mono- or poly-unsaturated aliphatic hydrocarbon radical containing the specified number of carbon atoms, or where no number is specified, preferably from 2-10 carbon atoms and more preferably, from 2-5 carbon atoms. Examples of alkenyl radicals include, but are not limited to, ethenyl, E- and Z-propenyl, E- and Z-isobutenyl, E- and Z-pentenyl, E- and

Z-hexenyl, E,E-, E,Z-, Z,E-, and Z-Z-hexadienyl and the like.

The term "alkynyl" or "alkyne", alone or in combination with any other term, refers to a straight-chain or branched-chain mono or poly-unsaturated aliphatic hydrocarbon radical containing the specified number of carbon atoms, or where no number is specified, preferably from 2-10 carbon atoms and more preferably, from 2-5 carbon atoms, wherein at least one of the unsaturated aliphatic hydrocarbon radicals comprises a triple bond. Examples of alkynyl radicals include, but are not limited to, ethynyl, propynyl, isobutynyl, pentynyl, hexynyl, hexenynyl, and the like.

The term "aryl", alone or in combination with any other term, refers to a carbocyclic aromatic radical containing the specified number of carbon atoms, and which may be optionally fused, for example benzofused, with one to three cycloalkyl, aromatic, heterocyclic or heteroaromatic rings. Preferred aryl groups have from 6-14 carbon atoms, and more preferred groups from 6-10 carbon atoms. Examples of aryl radicals include, but are not limited to, phenyl, naphthyl, anthracenyl and the like.

The term "carbocycle", alone or in combination with any other term, refers to a stable non-aromatic 3- to 8-membered carbon ring radical which may be saturated, mono-unsaturated or poly-unsaturated, and which may be optionally fused, for example benzofused, with one to three cycloalkyl, aromatic, heterocyclic or heteroaromatic rings. The carbocycle may be attached at any endocyclic carbon atom which results in a stable structure.

The terms "cycloalkyl" or "cycloalkane", alone or in combination with any other term, refers to a stable

non-aromatic 3- to 8-membered carbon ring radical which is saturated and which may be optionally fused, for example benzofused, with one to three cycloalkyl, aromatic, heterocyclic or heteroaromatic rings. The cycloalkyl may be attached at any endocyclic carbon atom which results in a stable structure. Preferred carbocycles have 5 to 6 carbons. Examples of carbocycle radicals include, but are not limited to, cyclopropyl, cyclbutyl, cyclpentyl, cyclohexyl, cycloheptyl, cyclopentenyl, cyclohexenyl, indane, tetrahydronaphthalene and the like.

The term "cycloalkenyl" or "cycloalkene" alone or in combination with any other term, refers to a stable cyclic hydrocarbon ring radical containing at least one endocyclic carbon-carbon double bond. The carbocycle may be attached at any cyclic carbon atom which results in a stable structure. Where no number of carbon atoms is specified, a cycloalkenyl radical preferably has from 5-7 carbon atoms. Examples of cycloalkenyl radicals include, but are not limited to, cyclopentenyl, cyclohexenyl, cyclopentadienyl, indenyl and the like.

The term "cycloalkylidenyl", alone or in combination with any other term, refers to a stable cyclic hydrocarbon ring radical containing at least one exocyclic carbon-carbon double bond, wherein the cyclic hydrocarbon ring may be optionally fused, for example benzofused, with one to three cycloalkyl, aromatic, heterocyclic or heteroaromatic rings. The carbocycle may be attached at any cyclic carbon atom, which results in a stable structure. Where no number of carbon atoms is specified, a cycloalkylidenyl radical preferably has from

5-7 carbon atoms. Examples of cycloalkylidenyl radicals include, but are not limited to, cyclopentylidenyl, cyclohexylidenyl, cyclopentenylidenyl and the like.

The skilled practitioner would realize that certain groups could be classified either as cycloalkanes or as aryl groups. Examples of such groups include indanyl and tetrahydro naphthyl groups.

The term "monocycle" or "monocyclic" alone or in combination with any other term, unless otherwise defined herein, refers to a 5-7 membered ring system.

The term "bicycle" or "bicyclic" alone or in combination with any other term, unless otherwise defined herein, refers to a 6-11 membered ring system.

The term "tricycle" or "tricyclic" alone or in combination with any other term, unless otherwise defined herein, refers to a 11-15 membered ring system.

The terms "heterocyclyl" and "heterocycle", alone or in combination with any other term, unless otherwise defined herein, refers to a stable 5- to 15-membered mono-, bi-, or tricyclic, heterocyclic ring which is either saturated or partially unsaturated, but not aromatic, and which may be optionally fused, for example benzofused, with one to three cycloalkyl, aromatic, heterocyclic or heteroaromatic rings. Each heterocycle consists of one or more carbon atoms and from one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. As used herein, the terms "nitrogen and sulfur heteroatoms" include any oxidized form of nitrogen and sulfur, and the quaternized form of any basic nitrogen. A heterocycle

may be attached at any endocyclic carbon or heteroatom which results in the creation of a stable structure.

Preferred heterocycles defined above include, for example, imidazolidinyl, indazolinolyl, perhydropyridazyl, pyrrolinyl, pyrrolidinyl, piperidinyl, pyrazolinyl, piperazinyl, morpholinyl, thiamorpholinyl, β-carbolinyl, thiazolidinyl, thiamorpholinyl sulfone, oxopiperidinyl, oxopyrroldinyl, oxoazepinyl, azepinyl, furazanyl, tetrahydropyranyl, tetrahydrofuranyl, oxathiolyl, dithiolyl, tetrahydrothiophenyl, dioxanyl, dioxolanyl, tetrahydrofurotetrahydrofuranyl, tetrahydropyranotetrahydrofuranyl, tetrahydrofurodihydrofuranyl, tetrahydropyranodihydrofuranyl, dihydropyranyl, dihydrofuranyl, dihydrofurotetrahydrofuranyl, dihydropyranotetrahydrofuranyl, sulfolanyl and the like.

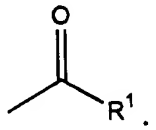
The terms "heteroaryl" and "heteroaromatic" alone or in combination with any other term, unless otherwise defined herein, refers to a stable 3- to 7-membered monocyclic heterocyclic ring which is aromatic, and which may be optionally fused, for example, benzofused, with one to three cycloalkyl, aromatic, heterocyclic or heteroaromatic rings. Each heteroaromatic ring consists of one or more carbon atoms and from one to four heteroatoms selected from the group consisting of nitrogen, oxygen and sulfur. As used herein, the terms "nitrogen and sulfur heteroatoms" include any oxidized form of nitrogen and sulfur, and the quaternized form of any basic nitrogen. A heteroaromatic ring may be attached at any endocyclic carbon or

heteroatom which results in the creation of a stable, aromatic structure.

Preferred heteroaromatics defined above include, for example, benzimidazolyl, imidazolyl, quinolyl, isoquinolyl, indolyl, indazolyl, pyridazyl, pyridyl, pyrrolyl, pyrazolyl, pyrazinyl, quinoxolyl, pyranyl, pyrimidinyl, pyridazinyl, furyl, thienyl, triazolyl, thiazolyl, tetrazolyl, benzofuranyl, oxazolyl, benzoxazolyl, isoxazolyl, isothiazolyl, thiadiazolyl, thiophenyl, and the like.

The term "halo" refers to a radical of fluorine, chlorine, bromine or iodine. Preferred halogen radicals include fluorine and chlorine.

In chemical formulas, parentheses are used herein to indicate 1) the presence of more than one atom or group bonded to the same atom or group; or 2) a branching point in a chain (i.e., the group or atom immediately before the open parenthesis is bonded directly to the group or atom immediately after the closed parenthesis). An example of the first use is "$N(R^1)_2$" denoting two R^1 groups bound to the nitrogen atom. An example of the second use is "$-C(O)R^1$" denoting an oxygen atom and a R^1 bound to the carbon atom, as in the following structure:

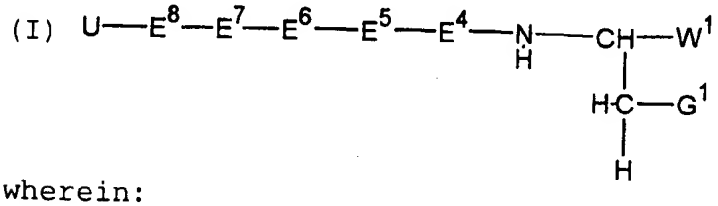


As used herein, "B" indicates a boron atom.

The present invention provides compounds that are useful as protease inhibitors, particularly as serine

protease inhibitors, and more particularly as HCV NS3 protease inhibitors. As such, they act by interfering with the life cycle of the HCV virus and other viruses that are dependent upon a serine protease for proliferation. Therefore, these compounds are useful as antiviral agents.

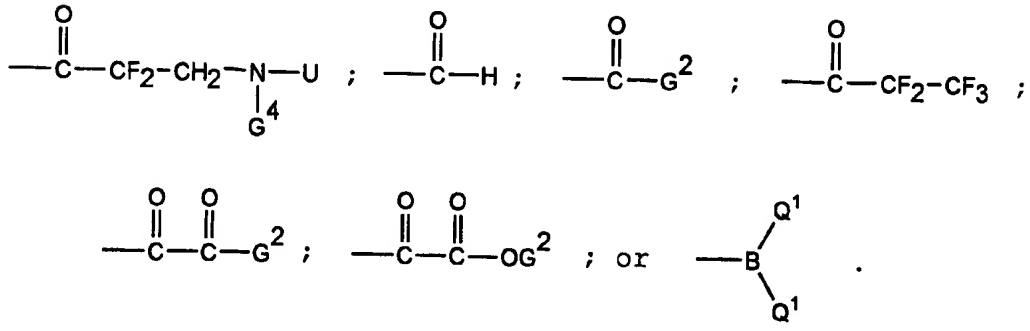
Accordingly, in one embodiment, the present invention provides a compound of the formula (I):

(I) 

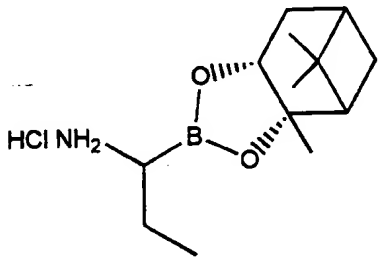
wherein:

G^1 is thiol, hydroxyl, thiomethyl, alkenyl, alkynyl, trifluoromethyl, C_{1-2} alkoxy, C_{1-2} alkylthio, or C_{1-3} alkyl, wherein the C_{1-3} alkyl group is optionally substituted with thiol, hydroxyl, thiomethyl, alkenyl, alkynyl, trifluoromethyl, C_{1-2} alkoxy, or C_{1-2} alkylthio.

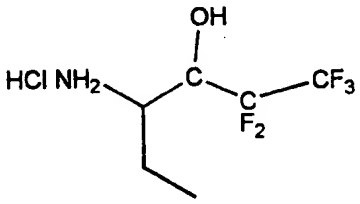
W^1 is:



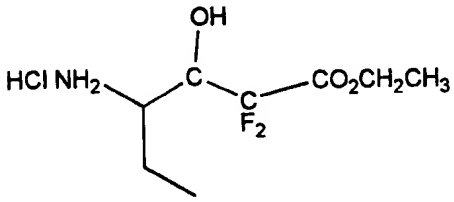
G^2 is alkyl, aryl, aralkyl, or a mono-, bi- or tricyclic heterocycle, optionally substituted with 1-3 groups selected from alkyl, alkenyl, alkynyl, aralkyl, alkoxy, alkenoxy, aryloxy, heterocyclyl,



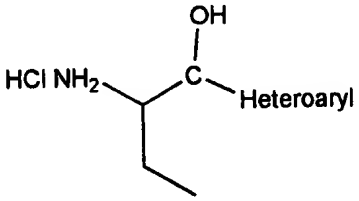
S. Elgendy et. al., Tetrahedron, 50, 3803-3812 (1994)



M. R. Angelestro et. al., Tetrahedron Letters, 33, 3265-3268 (1992)



T.T. Curran, J. Organic Chemistry, 58, 6360-6363 (1993)



E. Edwards, et. al., J. Medicinal Chemistry, 38, 3972-3982 (1995).

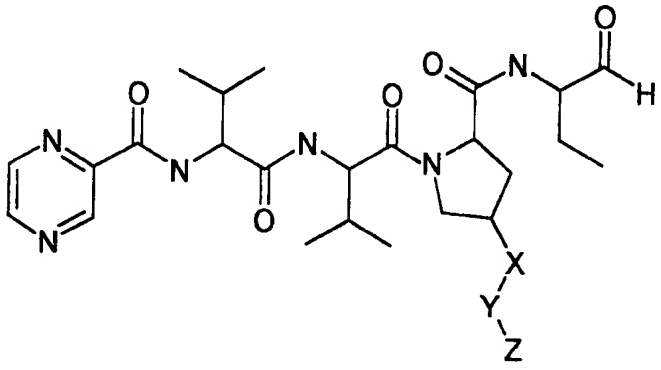
When required, the products obtained were oxidized to the ketones using Dess Martin Periodinane as described for Scheme 7. When required, acid labile protecting groups were removed by treatment with 1:1 trifluoroacetic

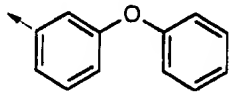
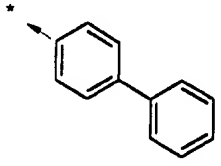
acid:dichloromethane at room temperature for 30 min. The solvent was removed in vacuo and the crude compound was purified by semi-prep RP-HPLC with a Waters DeltaPak 300 Å C18 column (15 μ, 30 X 300 mm) eluting with a linear acetonitrile gradient containing 0.1% TFA (v/v) over 45 min at 20 mL/min. Fractions containing the desired product were pooled and lyophilized to provide the final products 71-78 and 124-126.

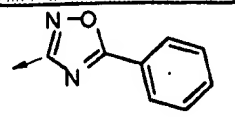
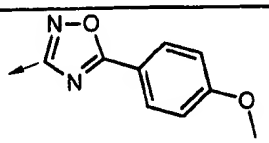
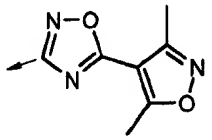
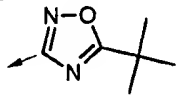
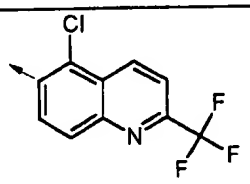
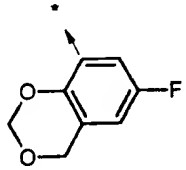
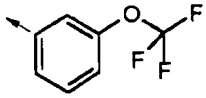
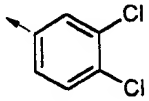
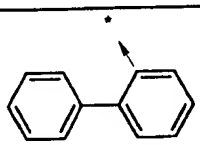
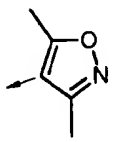
Example 10

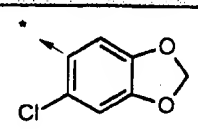
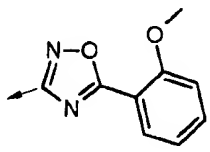
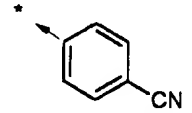
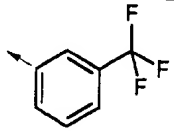
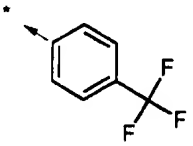
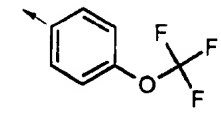
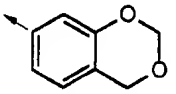
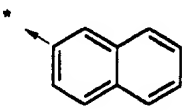
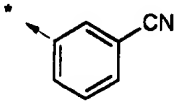
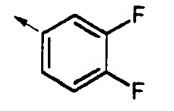
Compound 198 was prepared by modification of the general methodology described in Example 1.

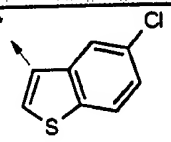
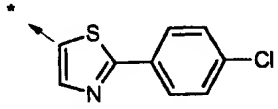
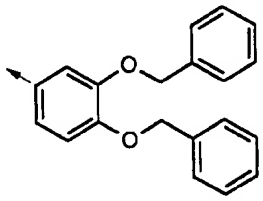
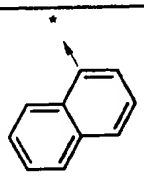
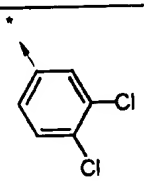
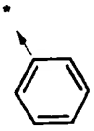
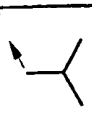
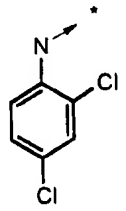
Table 1 Structures and analytical data - compounds 1-70.

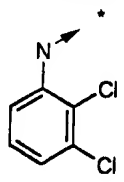
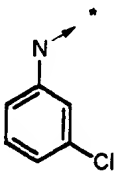
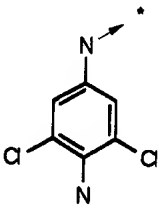
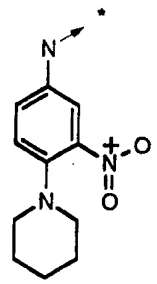
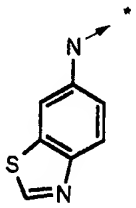
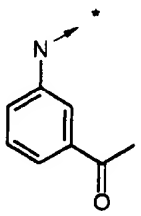


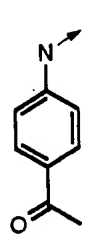
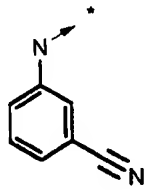
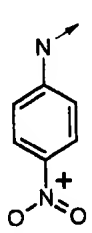
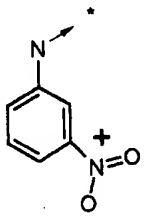
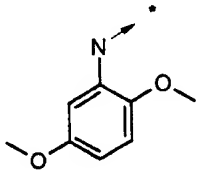
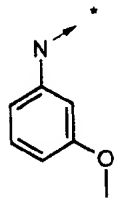
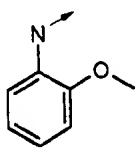
	Z	X	Y	MS Data	HPLC
1		O	CH_2	ND	40-80%B; 5.484 min.; 6.580 min; 75:25 fast:slow
2		O	CH_2	(M+Na)= 693.2	40-80%B; 5.376 min; 95%

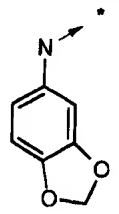
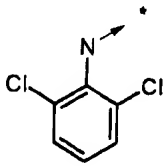
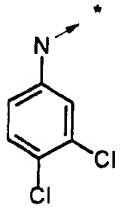
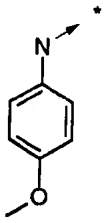
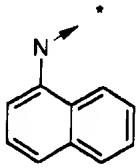
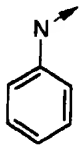
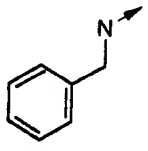
	Z	X	Y	MS Data	HPLC
3		O	CH_2	(M+H)= 664.0 (M+Na)= 685.2	20-60%B; 8.527 min.; 100%
4		O	CH_2	(M+Na)= 714.3	20-60%B; 8.885 min.; 100%
5		O	CH_2	(M+H)= 682.9 , (M+Na)= 704.0	20-60%B; 7.541 min.; 95.6%
6		O	CH_2	(M+H)= 644.0 , (M+Na)= 664.0	20-60%B; 7.822 min.; 100%
7		O	CH_2	(M+H)= 746.7 , (M+Na)= 765.7	40-80%B; 4.228 min.; 92%
8		O	CH_2	(M+H)= 671.5 , (M+Na)= 694.0	20-60%B; 8.554 min.; 98%
9		O	CH_2	(M+Na)= 700.9	40-80%B; 4.688 min.; 100%
10		O	CH_2	(M+Na)= 686.3	40-80%B; 4.630 min.; 94%
11		O	CH_2	(M+H)= 671.1, (M+Na)= 693.2	40-80%B; 5.323 min.; 6.435 min.; 88:12, fast:slow
12		O	CH_2	(M+H)= 613.7, (M+Na)= 636.2	20-60%B; 5.696 min.; 100%

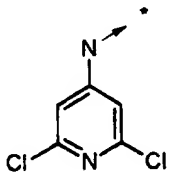
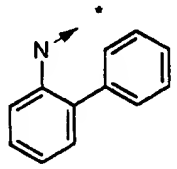
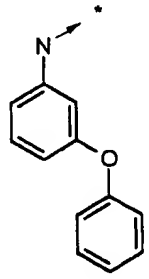
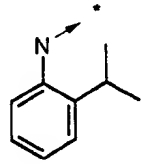
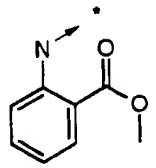
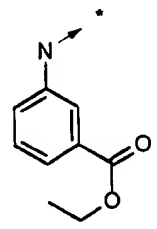
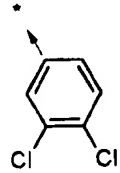
	Z	X	Y	MS Data	HPLC
13		O	CH_2	(M+Na)=695.3	20-60%B; 9.046 min.; 100%
14		O	CH_2	(M+Na)=714.9	20-60%B; 7.729 min.; 100%
15		O	CH_2	(M+Na)= 642.72	20-60%B; 7.133 min.; 100%
16		O	CH_2	(M+Na)= 685.6	20-60%B; 10.177 min.; 100%
17		O	CH_2	(M+Na)= 685.6	20-60%B; 10.265 min.; 100%
18		O	CH_2	(M+Na)= 700.9	20-60%B; 10.696 min.; 100%
19		O	CH_2	(M+Na)= 709.4	30-70%B; 9.216 min.; 100%
20		O	CH_2	(M+Na)= 667.3	20-60%B; 10.225 min; 100%
21		O	CH_2	(M+Na)= 641.8	20-60%B; 7.15 min.; 100%
22		O	CH_2	(M+Na)= 653.1	20-60%B; 8.822 min.; 100%

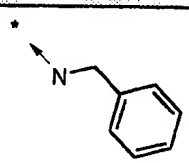
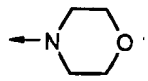
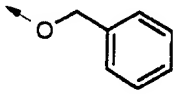
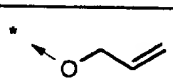
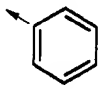
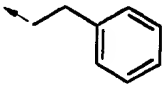
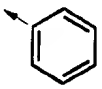
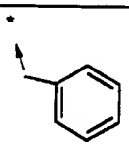
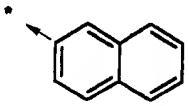
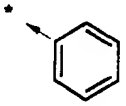
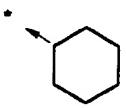
	Z	X	Y	MS Data	HPLC
23		O	CH_2	(M+Na)= 707.3	20-60%B; 11.362 min.; 100%
24		O	CH_2	(M+Na)= 733.9	20-60%B; 10.964 min.; 100%
25		O	CH_2	(M+Na)= 828.2	40-80%B; 7.040 min.; 100%
26		O	CH_2	(M+Na)= 667.5	30-70%B; 8.907 min.; 96%
27		O	C(O)	(M+H) = 677.3	10-60%B; 10.83 min; 80%
28		O	C(O)	(M+H) = 609.3	10-60%B; 9.65 min; 98%
29		O	C(O)	(M+H) = 589.6	10-60%B; 9.52 min; 98%
30		O	C(O)	(M+H) = 692.3	10-60% B; 11.52 min; 98% (slow RT); 10-60%B; 10.73 min; 90% (fast RT)

	Z	X	Y	MS Data	HPLC
31		O	C(O)	(M+H) = 692.3	10-60%B; 11.21 min; 98% (slow RT); 10-60%B; 10.23 min; 98%
32		O	C(O)	(M+H) = 658.4	10-60% B; 10.72 min; 98%
33		O	C(O)	(M+H) = 707.48	10-60%B; 9.9 min; 98%
34		O	C(O)	(M+H) = 752.6	10-60%B; 10.37 min; 98%
35		O	C(O)	(M+H) = 681.5	10-60%B; 8.40 min; 98%
36		O	C(O)	(M+H) = 666.6	10-60%B; 8.57 min; 86%

	Z	X	Y	MS Data	HPLC
37		O	C(O)	(M+H) = 666.6	10-60%B; 8.70 min; 86%
38		O	C(O)	(M+H) = 649.6	10-60%; 9.44 min; 98%
39		O	C(O)	(M+H) = 669.6	10-60%B; 10.06 min; 94%
40		O	C(O)	(M+H) = 669.6	10-60%B; 11.0 min; 96% (slow RT); 10-60%B; 10.12 min; 98% (fast RT)
41		O	C(O)	(M+H) = 684.6	10-60%B; 9.81 min; 95%
42		O	C(O)	(M+H) = 654.6	10-60%B; 9.52 min; 98%
43		O	C(O)	(M+H) = 654.6	10-60%B; 9.73 min; 93%

	Z	X	Y	MS Data	HPLC
44		O	C(O)	(M+H) = 668.56	10-60%B; 8.35 min; 92%
45		O	C(O)	(M+Na) = 716.5	10-60%B; 8.86 min; 80%
46		O	C(O)	(M+Na) = 716.1	10-60%B; 11.26/11.58 min (1:7); 98%; 10-60%B; 11.27/11.56 min (2:1); 98%
47		O	C(O)	(M+Na) = 678.1	10-60%B; 8.33 min; 96%
48		O	C(O)	(M+Na) = 697.8	10-60%B; 9.73 min; 90%
49		O	C(O)	(M+Na) = 647.2	10-60%B; 8.59 min; 90%
50		O	C(O)	(M+Na) = 660.6	10-60%B; 8.36 min; 94%

	Z	X	Y	MS Data	HPLC
51		O	C(O)	(M+H) = 693.3	10-60%B; 9.42 min/10.37 min; 85%
52		O	C(O)	(M+H) = 700.4	10-60%B; 10.59 min; 98%
53		O	C(O)	(M+H) = 716.3	10-60%B; 11.24/12.18 min; 95%
54		O	C(O)	(M+H) = 666.4	10-60%B; 9.97 min; 98%
55		O	C(O)	(M+H) = 682.3	10-60%B; 9.89 min; 98%
56		O	C(O)	(M+H) = 696.3	10-60%B; 10.34 min; 98%
57		NH	C(O)	(M+H) = 676.31	20-60%B; 9.023 min.; 100%

	Z	X	Y	MS Data	HPLC
58		NH	C(O)	(M+H)= 637.5	20-80%B; 5.152 min.; 100%
59		NH	C(O)	(M+H)= 617.5	20-80%B; 3.216 min.; 100%
60		NH	C(O)	(M+H)= 638.5	20-80%B; 6.221 min.; 100%
61		NH	C(O)	(M+H)= 588.4	20-80%B; 4.503 min.; 100%
62		NH	C(O)	(M+H)= 608.5	20-80%B; 5.055 min.; 100%
63		NH	C(O)	(M+H)= 636.5	20-80%B; 5.697 min.; 100%
64		NH	C(O) C(O)	(M+H)= 636.5	20-80%B; 5.548 min.; 100%
65		NH	$S(O)_2$	(M+H)= 658.4	20-80%B; 5.632 min.; 100%
66		NH	C(O)	(M+H)= 658.5	20-80%B; 6.690 min.; 100%
67		NH	CH_2	(M+H)= 594.5	20-80%B; 5.114 min.; 100%
68		NH	C(O)	(M+H)= 614.5	20-80%B; 5.559 min.; 100%

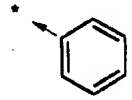
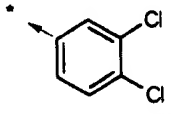
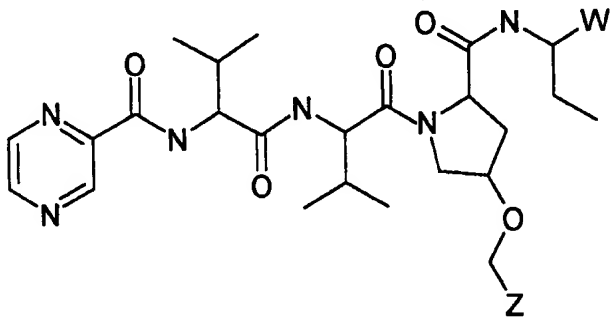
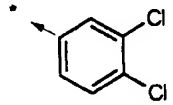
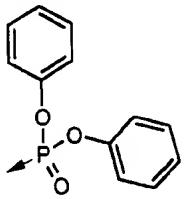
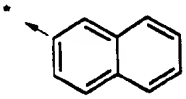
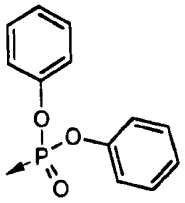
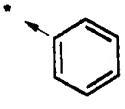
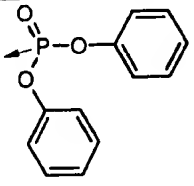
	Z	X	Y	MS Data	HPLC
69		O	CH_2	(M+H)=560.4	20-80%B; 8.062 min.; 100%
70		O	CH_2	(M+H)= 628.3	20-80%B; 9.990 min.; 100%

Table 2 Structures and analytical data - compounds 71-79



	Z	W	MS Data	HPLC
71			(M+H)= 869.3	40-80%B; 8.812:8.920 min.; 2:1 mix at Abu; 100%
72			(M+H)= 849.4	40-80%B; 8.380:8.539 min.; 2:1 mix at Abu; 100%
73			(M+H)= 799.5	20-60%B; 12.519 min.; 95%

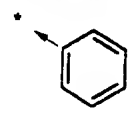
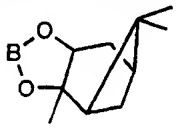
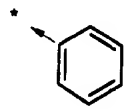
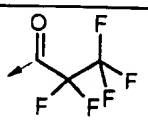
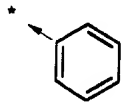
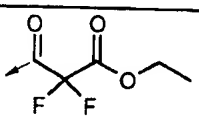
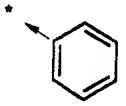
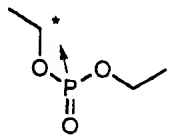
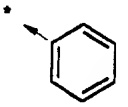
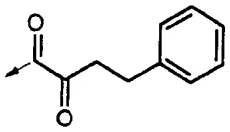
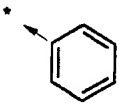
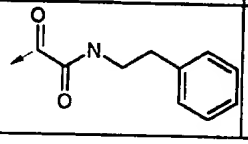
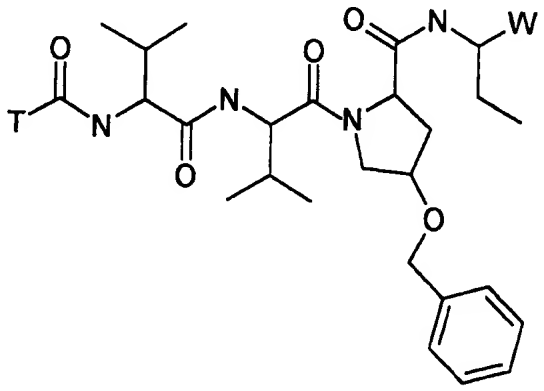
	Z	W	MS Data	HPLC
74			(M+H)= 716	15.62 min.; >95%
75			(M+H)=713	13.47 min.
76			(M+H)=717	13.05 min.; >90%
77			(M+H)= 703	10-90%B; 8.5 min.; 8.6 min (2:1); >95%
78			(M+H)= 727	8.7 min.; 10 min. (2:1); 95%
79			(M+H)= 743	10-80%B; 5.4 min.; 95%

Table 3 Structures and analytical data - compounds 80-88



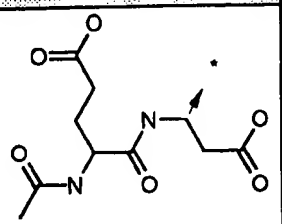
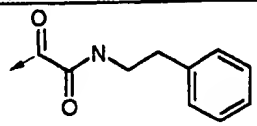
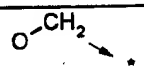
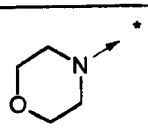
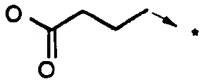
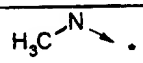
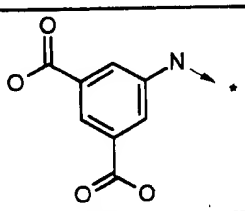
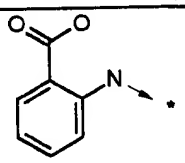
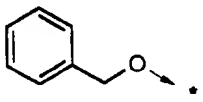
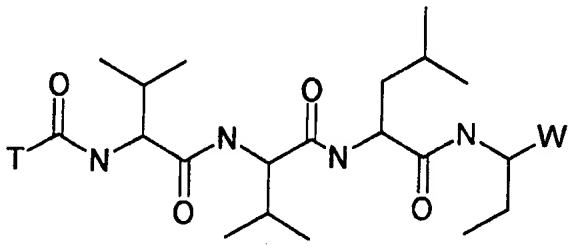
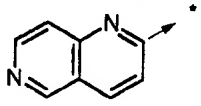
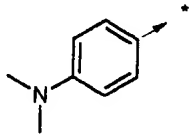
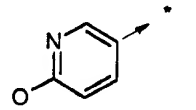
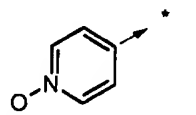
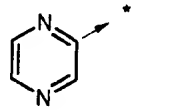
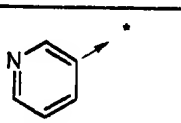
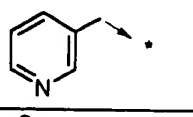
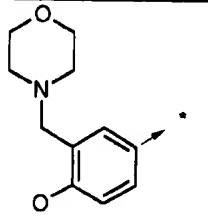
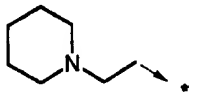
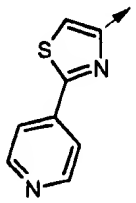
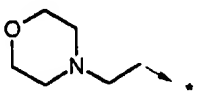
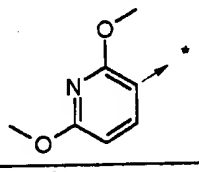
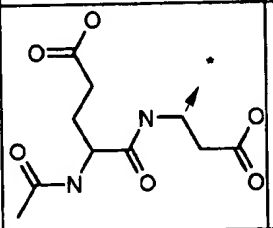
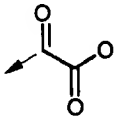
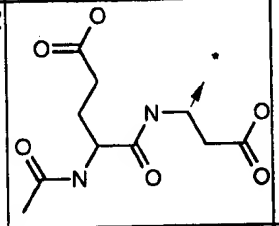
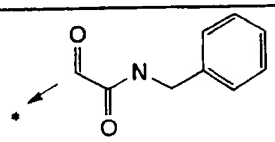
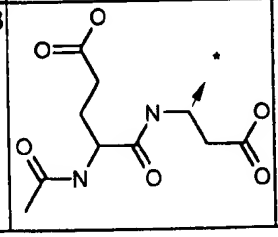
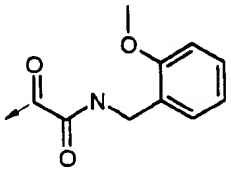
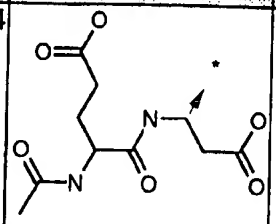
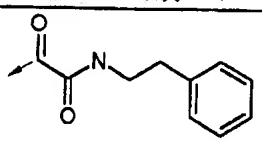
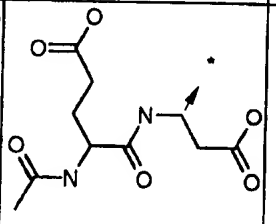
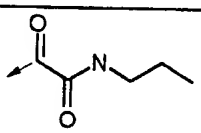
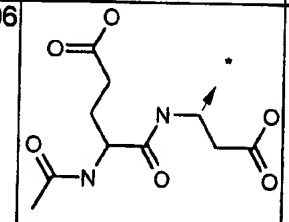
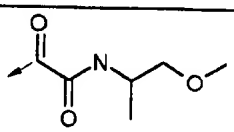
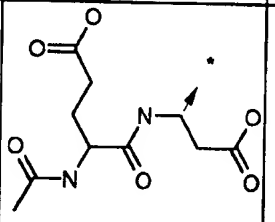
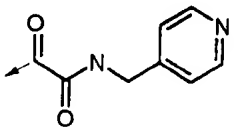
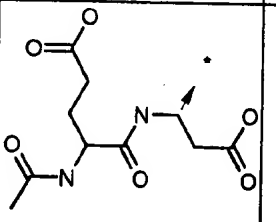
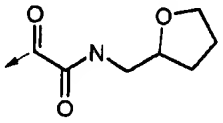
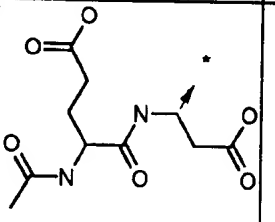
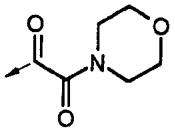
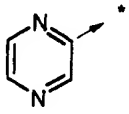
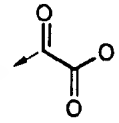
	T	W	MS Data	HPLC
80			(M+H)= 947	20-70%B; 6.15 min.; 95%
81		C(O)H	(M+Na)= 553.60	5-45%B; 11.699 min.; 100%
82		C(O)H	(M+H)= 547.4	5-45%B; 11.083 min.; 100%
83		C(O)H	(M+Na)= 625.3	5-45%B; 12.258 min.; 100%
84		C(O)H	(M+Na)= 626.5	5-45%B; 11.083 min.; 100%
85		C(O)H	(M+Na)= 569.5	5-45%B; 11.606 min.; 100%
86		C(O)H	(M+Na)= 717.2	5-45%B; 7.942 min.; 100%
87		C(O)H	(M+H)= 655.3	15-55%B; 10.735 min.; 100%
88		C(O)H	(M+Na)= 644.1	20-60%B; 11.360 min.; 98%

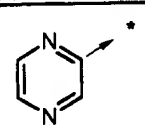
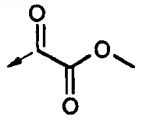
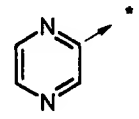
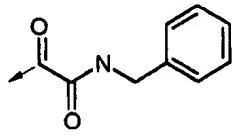
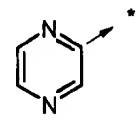
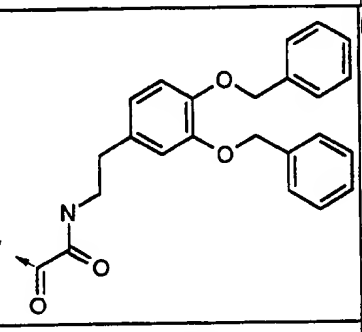
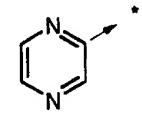
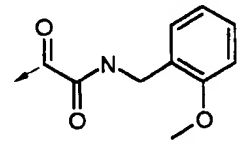
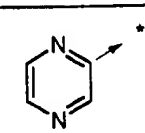
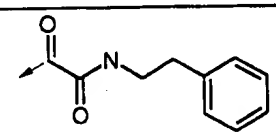
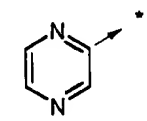
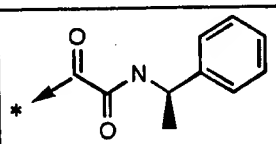
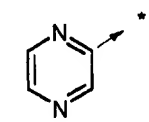
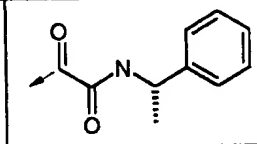
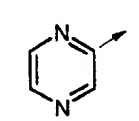
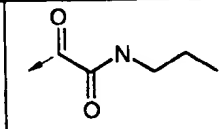
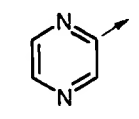
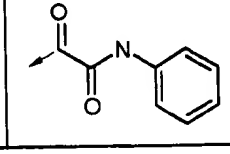
Table 4 Structures and analytical data - compounds 89-126



	T	W	MS Data	HPLC
89		C(O)H	(M+H)= 555.9	5-45% B; 10.771 min.; 99%
90		C(O)H	(M+H)= 556.0	5-45% B; 13.055 min.;95%
91		C(O)H	(M+H)= 522.4	5-45%B; 9.485 min.; 97%
92		C(O)H	(M+H)= 522.55	5-45%B; 9.072 min.; 100%
93		C(O)H	(M+H)= 506.33	5-45%B; 11.775 min.; 97%
94		C(O)H	(M+Na)= 526.6	5-45%B; 8.822 min.; 100%
95		C(O)H	(M+H)= 518.	5-45%B; 8.484 min.; 100%
96		C(O)H	(M+H)= 619.6	5-45%B; 9.944 min.; 90%

	T	W	MS Data	HPLC
97		C(O)H	(M+H)= 538.7	5-45%B; 9.099 min.; 100%
98		C(O)H	(M+H)= 588.6	5-45%B; 10.388 min.; 95%
99		C(O)H	(M+H)= 541.1	5-45%B; 8.326 min.; 100%
100		C(O)H	(M+Na)= 587.3	35-75%B; 6.763 min.; 95%
101			(M+H)= 729	10-80%B; 3.0 min; 95%
102			(M+H)= 819; (M+Na)= 840	20-70%B; 6.9 min; 95%
103			(M+H)=848; (M+Na)= 870	20-70%B; 6.3 min; 95%

	T	W	MS Data	HPLC
104			(M+H)= 833	20-70%B; 7.3 min; 95%
105			(M+H)=770; (M+Na)=792	20-70%B; 6.0 min; 95%
106			(M+H)= 801; (M+Na)= 822	20-70%; 5.9 min; 95%
107			(M+H)=819; (M+Na)= 841	20-70%B; 3.24 min; 95%
108			(M+H)=812; (M+Na)=834	20-70%B; 4.9 min; 95%
109			(M+H)=798; (M+Na)=820	20-70%B; 4.21 min; 95%
110			(M+H)= 550	10-40%B; 7.0 min; 95%

	T	W	MS Data	HPLC
111			(M+Na)= 886	10-50%B; 7.5 min; 95%
112			(M+H)= 638	10-80%B; 6.5 min; 95%
113			(M+H)= 865	40-80%B; 5.7 min; 95%
114			(M+H)= 669; (M+Na)= 693	25-40%B; 11.6 min; 95%
115			(M+H)= 653	10-80%B; 6.80 min; 95%
116			(M+H)= 653	10-80%B; 6.7 min; 95%
117			(M+H)= 653	10-80%B; 6.7 min; 95%
118			(M+Na)= 611	10-80%B; 5.62 min; 95%
119			(M+H)= 624	10-80%B; 12.1 min; 95%

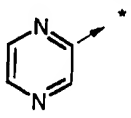
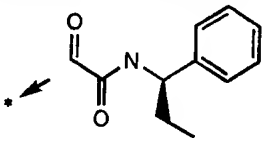
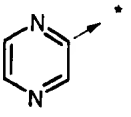
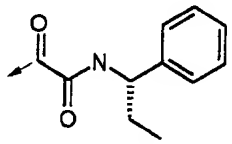
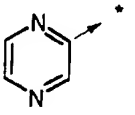
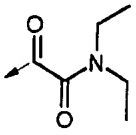
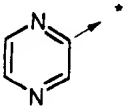
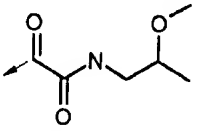
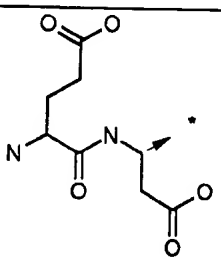
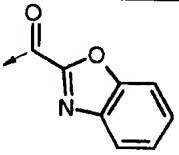
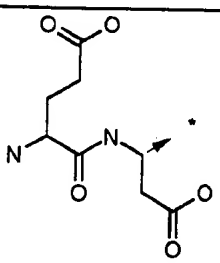
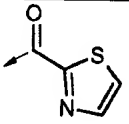
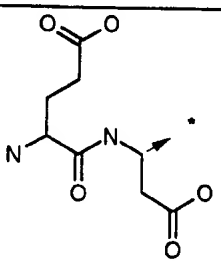
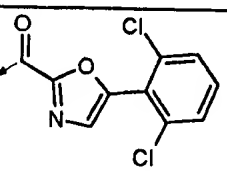
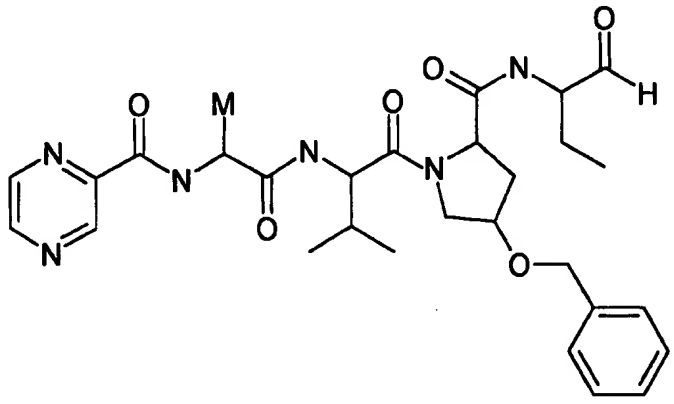
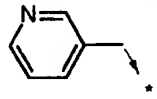
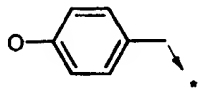
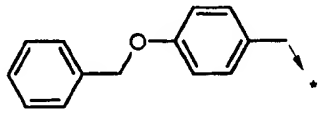
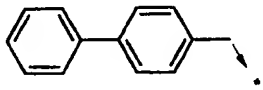
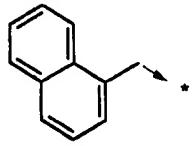
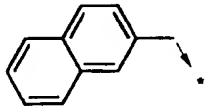
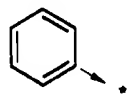
	T	W	MS Data	HPLC
120			(M+H)= 667	10-80%B; 13.4 min; 95%
121			(M+H)= 667	10-80%B; 13.3 min; 95%
122			(M+H)= 605	10-80%B; 11.0 min; 95%
123			(M+H)= 621	10-80%B; 9.7 min; 95%
124			(M+H)= 761	13.65 min.; 90%
125			(M+H)= 727	ND
126			(M+H)= 856	ND

Table 5 Structures and analytical data - compounds 127-142



	M	MS Data	HPLC
127		(M+H)= 644.30	15-55%B; 6.08 min; 100%
128		(M+H)= 681.3	20-60%B; 8.11 min; 100%
129		(M+H)= 750.6	30-70%B; 6.99 min; 100%
130		(M+H)= 720.2	30-70%B; 6.71 min; 100%
131		(M+Na)= 715.4	30-70%B; 5.64 min; 100%
132		(M+Na)= 715.2	30-70%B; 5.58 min; 100%
133		(M+H)= 630.9	30-70%B; 3.78 min; 100%

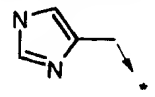
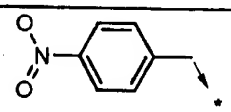
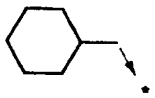
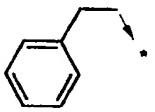
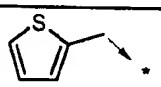
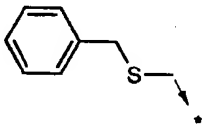
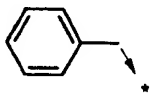
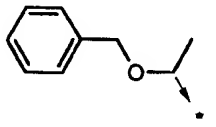
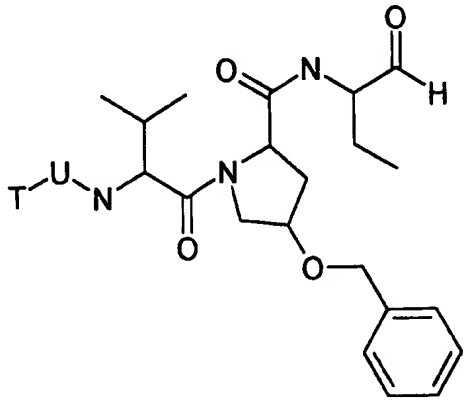
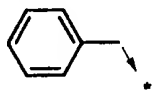
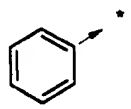
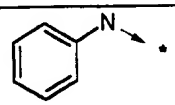
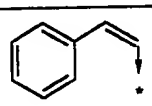
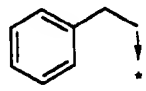
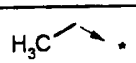
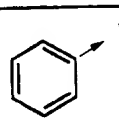
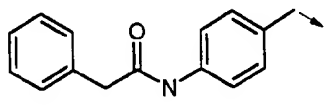
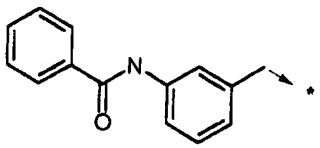
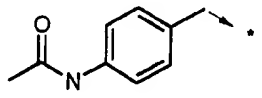
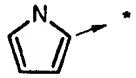
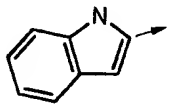
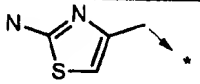
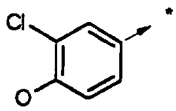
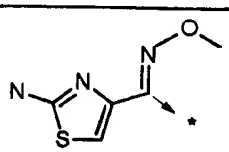
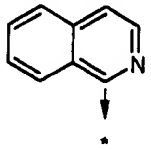
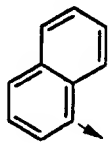
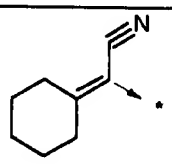
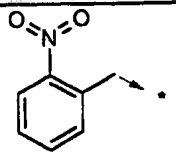
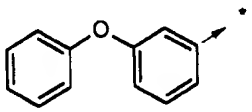
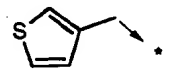
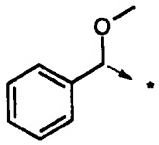
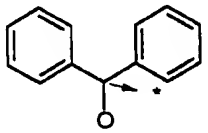
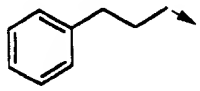
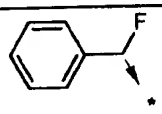
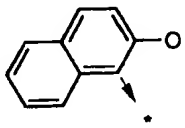
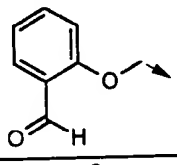
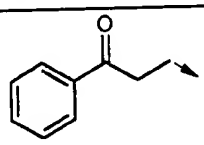
	M	MS Data	HPLC
134		(M+H)= 634.0	15-55%B; 5.90 min; 100%
135		(M+H)= 691.60	30-70%B; 4.22 min; 100%
136		(M+H)= 651.20	40-80%B; 5.59 min; 100%
137		(M+H)= 659.10	40-80%B; 4.65 min; 100%
138		(M+H)= 651.70	40-80%B; 3.83 min; 100%
139		(M+H)= 582.90	40-80%B; 2.34 min; 100%
140		(M+H)= 690.70	40-80%B; 5.15 min; 100%
141		(M+Na)= 664.80	40-80%B; 3.93 min; 100%
142		(M+Na)= 708.80	40-80%B; 5.398 min; 100%

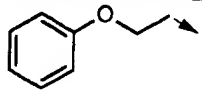
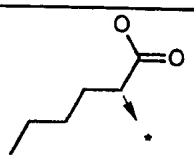
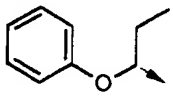
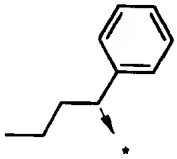
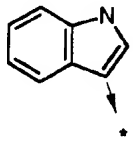
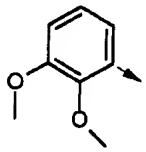
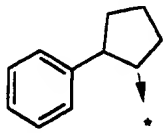
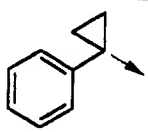
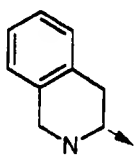
Table 6 Structures and analytical data - compounds 143-197

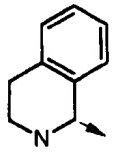
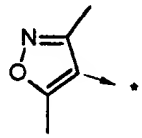
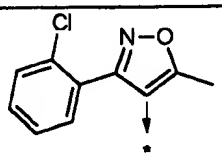
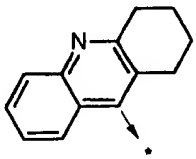
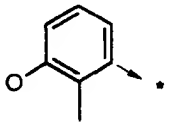
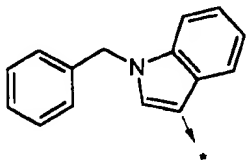
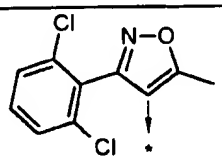
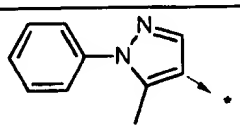
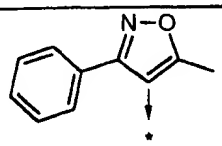


	T	U	MS Data	HPLC
143		$S(O_2)$	(M+Na)= 566.71	20-80%B; 10.186 min.; >95%
144		$S(O_2)$	(M+Na)= 552.26	20-80%B; 9.985 min.; 90%
145		C(O)	(M+Na)= 531.60	20-80%B; 9.978 min; 95%
146		C(O)	(M+Na)= 542.37	20-80%B; 10.404 min; 95%
147		C(O)	(M+Na)= 544.42	20-80%B; 10.246 min; 95%
148		C(O)	(M+Na)= 454.26	20-80%B; 7.109 min; 95%
149		C(O)	(M+Na)= 516.05	20-80%B; 9.668 min; 95%
150		C(O)	(M+Na)= 649.17	20-80%B; 9.880 min; 95%

	T	U	MS Data	HPLC
151		C(O)	(M+Na)= 648.45	20-80%B; 10.030 min; 95%
152		C(O)	(M+Na)= 587.08	20-80%B; 7.892 min; 95%
153		C(O)	(M+Na)= 505.47	20-80%B; 8.583 min; 95%
154		C(O)	(M+Na)= 554.96	20-80%B; 10.411 min; 95%
155		C(O)	(M+Na)= 551.90	20-80%B; 6.737 min; 95%
156		C(O)	(M+Na)= 566.11	20-80%B; 9.227 min; 95%
157		C(O)	(M+Na)= 594.59	20-80% B; 7.567 min; 95%
158		C(O)	(M+Na)= 567.00	20-80%B; 10.409 min; 95%
159		C(O)	(M+Na)= 566.10	20-80%B; 10.716 min; 95%
160		C(O)	(M+Na)= 559.27	20-80%B; 10.597 min; 95%

	T	U	MS Data	HPLC
161		C(O)	(M+Na)= 574.66	20-80%B; 9.723 min; 95%
162		C(O)	(M+Na)= 607.43	20-80%B; 12.019 min; 95%
163		C(O)	(M+H)= 514.83	20-80%B; 6.170 min; 95%
164		C(O)	(M+H)= 538.87	20-80%B; 7.094 min; 99%; 20-80%B; 6.712 min; 99%
165		C(O)	(M+Na)= 620.77	20-80%B; 8.390 min; 99%
166		C(O)	(M+H)= 536.44	20-80%B; 7.787 min; 99%
167		C(O)	(M+H)= 525.58	20-80%B; 7.023 min; 99%
168		C(O)	(M+Na)= 582.25	20-80%B; 7.220 min; 98%
169		C(O)	(M+H)= 552.32	20-80%B; 6.410 min; 99%
170		C(O)	(M+H)= 550.77	20-80%B; 6.663 min; 99%

	T	U	MS Data	HPLC
171		C(O)	(M+H)= 538.87	20-80%B; 7.101 min; 99%
172		C(O)	(M+Na)= 554.79	20-80%B; 7.011 min; 99%
173		C(O)	(M+H)= 551.59	20-80%B; 8.029 min; 96%
174		C(O)	(M+H)= 549.86	20-80%B; 7.320 min; 99%
175		C(O)	(M+Na)= 554.79	20-80%B; 6.413 min; 99%
176		C(O)	(M+H)= 555.05	20-80%B; 7.065 min; 99%
177		C(O)	(M+Na)= 584.55	20-80%B; 9.099 min; 99%
178		C(O)	(M+H)= 535.23	20-80%B; 8.038 min; 99%
179		C(O)	(M+Na)= 569.07	10-80%B; 5.885; 98%

	T	U	MS Data	HPLC
180		C(O)	(M+H)= 548.03	10-80% B; 5.991; 99%
181		C(O)	(M+Na)= 533.91	10-80%B; 7.237; 99%
182		C(O)	(M+Na)= 630.91	10-80%B; 9.382; 95%
183		C(O)	(M+H)= 599.4	10-80% B; 7.0 min; 99%
184		C(O)	(M+Na)= 545.27	10-80%B; 6.89 min; 99%
185		C(O)	(M+Na)= 643.91	10-80%B; 10.43 min; 99%
186		C(O)	(M+Na)= 664.69	10-80%B; 9.95 min; 99%
187		C(O)	(M+Na)= 595.53	10-80%B; 8.61 min; 99%
188		C(O)	(M+Na)= 596.45	10-80%B; 9.0 min; 92%

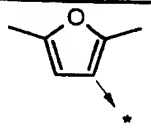
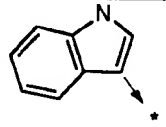
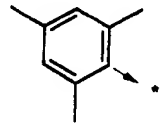
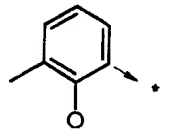
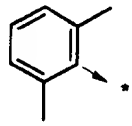
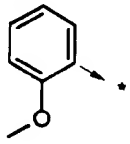
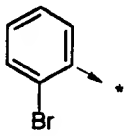
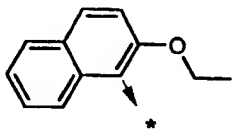
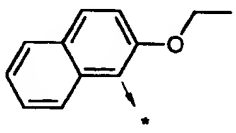
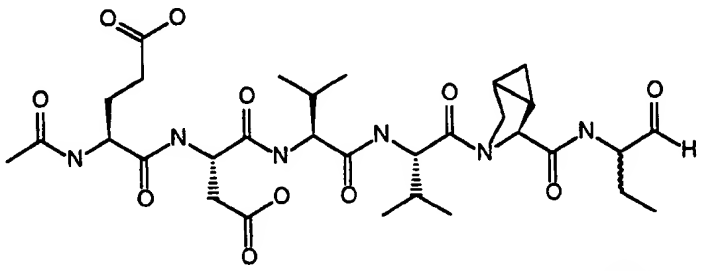
	T	U	MS Data	HPLC
189		C(O)	(M+Na)= 533.73	10-80%B; 8.438; 99%
190		C(O)	(M+Na)= 554.20	10-80%B; 7.990; 99%
191		C(O)	(M+Na)= 557.74	10-80%B; 9.06 min; 99%
192		C(O)	(M+Na)= 545.70	10-80%B; 10.11 min; 99%
193		C(O)	(M+Na)= 544.06	10-80%B; 8.41 min; 99%
194		C(O)	(M+Na)= 545.49	10-80%B; 8.41 min; 96%
195		C(O)	(M+Na)= 594.05	10-80%B; 8.3 min; 99%
196		C(O)	(M+H)= 574.3	10-80%B; 8.84 min; 98%
197		C(O)	(M+H)= 588.4	10-80%B; 9.37 min; 99%

Table 7 Structure and analytical data - compound 198.



	MS Data	HPLC
198	(M+Na)= 702.4	10-60%B; 4.2 min.; >95%

Example 11

Insofar as compounds of formula (I) or (II) are able to inhibit NS3 serine protease, they are of evident clinical utility for the treatment of viral diseases, including HCV. These tests are predictive of the compounds ability to inhibit HCV in vivo.

Peptides and Assays.

Peptides EDVV abuCSMSY (Abu designates - aminobutyric acid), DEMEECSQHLPYI, ECTTPCSGSWLRD and EDVV AbuC-p-nitroanilide was purchased from AnaSpec Inc. (San Jose, CA).

Peptide content of purified, lyophilized peptides and in-house peptides was determined by quantitative nitrogen analysis and the appropriate values were used in preparing stock peptide solutions (Galbreath). pKa determinations were determined by Robertson Microlit Laboratories, Inc. (Madison, NJ).

HPLC cleavage assays were performed using 25 nM to 3.0 μM enzyme in 100 μL volumes at 30 C containing 50 mM HEPES-KOH (pH 7.8), 100 mM NaCl, 20% glycerol, 5 mM DTT and the appropriate amount of substrate (in DMSO),

with or without NS4A peptide, such that the final concentration of DMSO did not exceed 4%. Separate control experiments verified that this percentage of DMSO did not effect enzymatic activity. Cleavage reactions were quenched by the addition of an equal volume of a mixture of 10% TFA: acetonitrile (1:1) and activity was assessed on a reversed phase HPLC column (Rainin C18 Microsorb-MV, 5mm, 4.6 x 250mm; 0-50% acetonitrile, 0.1% TFA @ 3.33% min) using a Hewlett Packard 1050 instrument with auto-injection and diode array detection at 210 nm and 280 nm (where appropriate). Peptide elution fragments were collected and identified by mass spectrometry and N-terminal sequence analysis. Fragment identity and concentration was further verified by authentic, synthesized products. Initial rates of cleaveage were determined at < 20% substrate conversion and catalytic parameters were determined assuming Michaelis-Menten kinetics using the MultiFit program (Day Computing, Cambridge, MA).

Spectrophotometric assays were run in a 96-well microtiter plate at 30 C, using a SpectraMax 250 reader (Molecular Devices, Sunnyvale, CA) with kinetic capability. Cleavage of EDVV AbuC-p-nitroanilide (5A-pNA) substrate was performed with or without NS44 in the same buffer used for HPLC assays at 30 C, and pNA release was monitored at 405 nm. The extinction coefficient of p-nitroaniline is independent of pH at values of 5.5. and above [Tuppy , H., et al., Hoppe-Seyler's Z. Physiol. Chem., 329, pp. 278-288 (1962)]; Raybuck and Luong, unpublished obervations). The percentage of DMSO did not exceed 4% in these assays.

Determination of the pH dependence of Vmax, K_m and V_{max}/K_m was performed using a series of constant ionic strength buffers containing 50 mM MES, 25 Nm Tris, 25 mM ethanolamine and 0.1 M NaCl [Morrison, J.F. and Stone,

R.F., Biochemistry, 27, pp. 5499-5506 (1988)]. The inflection point for log V data was calculated by nonlinear least squares fit of the data to the equation.

$$\log v = \log[Vmax/(1 + H/K_a)]$$

[Dixon, M. and Webb, E. C. Enzymes; Academic Press: New York; Vol., pp. 138-164 (1979)]. The inflection points for log (V/K) data were calculated by nonlinear least squares fit of the data to the equation

$\log v = \log[Vmax/(1 + H/K_a + K_b/H)]$ [Dixon, M. and Webb, E. C. Enzymes; Academic Press: New York; Vol., pp. 138-164 (1979)]. The program KineTic (BioKin Ltd) was used in both cases.

Kinetic constants for the rapid equilibrium ordered bisubstrate reaction were determined from rate *vs* [4A], [EDVV AbuC-pNA] data by non-linear least squares fitting to equation 1 [Morrison, J.F. Biochim. Biophys. Acta., 185, pp. 269-286 (1969)] as described in the text. K_{ii} and K_{is} values for peptidyl inhibitors were determined from rate *vs* [inhibitor], [substrate] data and fitting to the equation for mixed inhibition:

$$\text{rate} = Vmax[S]/\{Km(1+[I]/Kis) + [S] (1 + [I]/Kii)\}$$

The commercial program KinetAsyst (StateCollege, PA) was used for both procedures. Ki values were calculated from rate *vs* [inhibitor] plots by a nonlinear least squares fit of the data to the equation of Morrison for tight binding competitive inhibition [Morrison, J.F. Biochim. Biophys. Acta., 185, pp. 269-286 (1969)]. The KineTic program (BioKin Ltd) was used for this procedure.

The results are shown in Table 9. K_i values are expressed in μM. Category "A" indicates < 1 μM inhibition; category "B" indicates 1-100 μM inhibition; category "C" indicates > 100 μM. The designation "ND" indicates that the compound was not tested.

Table 9. Enzyme inhibition data for compounds 1-198.

Cmpd. No.	Ki (μM)	Cmpd. No.	Ki (μM)	Cmpd. No.	Ki (μM)
1	B	42	B	83	B
2	B	43	B	84	B
3	B	44	B	85	B
4	B	45	B	86	B
5	B	46	B	87	B
6	B	47	B	88	B
7	B	48	B	89	B
8	B	49	B	90	B
9	B	50	B	91	B
10	B	51	B	92	B
11	B	52	B	93	B
12	B	53	B	94	B
13	B	54	B	95	B
14	B	55	B	96	B
15	B	56	C	97	B
16	B	57	B	98	B
17	B	58	B	99	B
18	B	59	B	100	B
19	B	60	C	101	A
20	B	61	C	102	A
21	B	62	B	103	A
22	B	63	B	104	A
23	B	64	B	105	A
24	B	65	B	106	A
25	B	66	B	107	A
26	B	67	C	108	A
27	B	68	C	109	B
28	B	69	B	110	B
29	B	70	B	111	C
30	B	71	A	112	B
31	B	72	B	113	B
32	B	73	B	114	C
33	C	74	B	115	B
34	B	75	B	116	B
35	B	76	C	117	B
36	C	77	C	118	B
37	B	78	B	119	C
38	B	79	B	120	B
39	B	80	A	121	C
40	B	81	B	122	C
41	B	82	B		

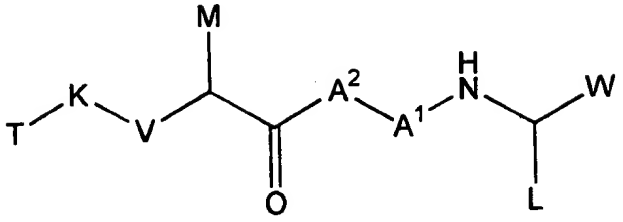
Cmpd. No.	Ki (μM)	Cmpnd. No.	Ki (μM)	Cmpnd No.	Ki (μM)
123	B	149	B	174	B
124	B	150	B	175	B
125	B	151	C	176	C
126	C	152	C	177	C
127	C	153	B	178	C
128	B	154	B	179	B
129	B	155	B	180	C
130	C	156	B	181	C
131	B	157	B	182	C
132	B	158	B	183	B
133	B	159	B	184	B
134	C	160	B	185	B
135	B	161	C	186	C
136	B	162	B	187	C
137	B	163	C	188	C
138	B	164	C	189	C
139	C	165	C	190	C
140	B	166	C	191	C
141	B	167	C	192	C
142	B	168	B	193	C
143	C	169	C	194	C
144	C	170	C	195	B
145	B	171	C	196	B
146	B	172	C	197	B
147	C	173	C	198	A
148	C				

While we have hereinbefore presented a number of embodiments of this invention, it is apparent that my basic construction can be altered to provide other embodiments which utilize the methods of this invention. Therefore, it will be appreciated that the scope of this invention is to be defined by the claims appended hereto rather than the specific embodiments which have been presented hereinbefore by way of example.

CLAIMS

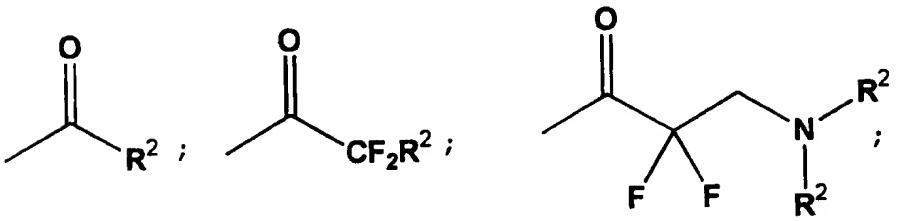
What is claimed is:

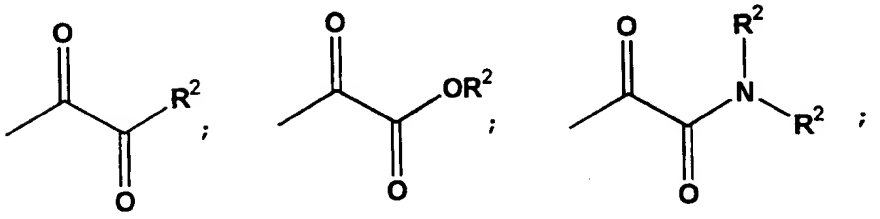
1. A compound of the formula (II):

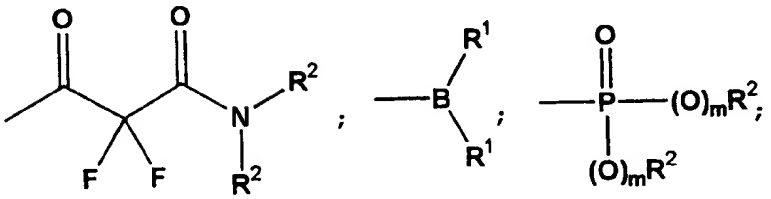
(II) 

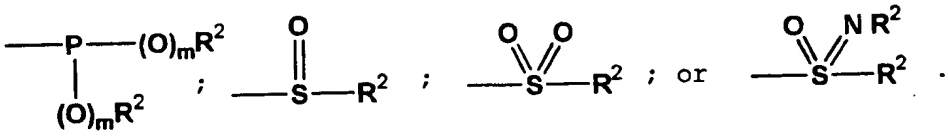
, wherein

W is:









m is 0 or 1;

each R^1 is hydroxy, alkoxy, or aryloxy, or each R^1 is an oxygen atom and together with the boron, to which they are each bound, form a 5-7 membered ring, wherein the ring atoms are carbon, nitrogen, or oxygen;

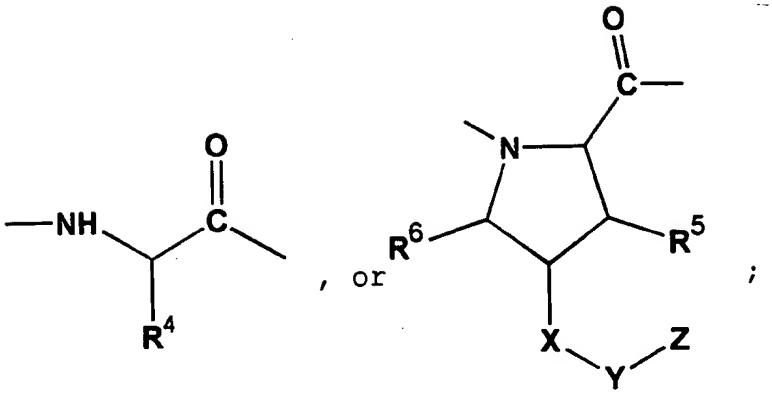
each R^2 is independently hydrogen, alkyl, alkenyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, cycloalkenylalkyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkenyl, heteroaryl, or heteroaralkyl, or two R^2 groups, which are bound to the same nitrogen atom, form together with that nitrogen atom, a 5-7 membered monocyclic heterocyclic ring system; wherein any R^2 carbon atom is optionally substituted with J;

J is alkyl, aryl, aralkyl, alkoxy, aryloxy, aralkoxy, cycloalkyl, cycloalkoxy, heterocyclyl, heterocyclyloxy, heterocyclylalkyl, keto, hydroxy, amino, alkylamino, alkanoylamino, aroylamino, aralkanoylamino, carboxy, carboxyalkyl, carboxamidoalkyl, halo, cyano, nitro, formyl, acyl, sulfonyl, or sulfonamido and is optionally substituted with 1-3 J^1 groups;

J^1 is alkyl, aryl, aralkyl, alkoxy, aryloxy, heterocyclyl, heterocyclyloxy, keto, hydroxy, amino, alkanoylamino, aroylamino, carboxy, carboxyalkyl, carboxamidoalkyl, halo, cyano, nitro, formyl, sulfonyl, or sulfonamido;

L is alkyl, alkenyl, or alkynyl, wherein any hydrogen is optionally substituted with halogen, and wherein any hydrogen or halogen atom bound to any terminal carbon atom is optionally substituted with sulfhydryl or hydroxy;

A^1 is a bond,



R^4 is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, carboxyalkyl, or carboxamidoalkyl, and is optionally substituted with 1-3 J groups;

R^5 and R^6 are independently hydrogen, alkyl, alkenyl, aryl, aralkyl, aralkenyl, cycloalkyl, cycloalkylalkyl, cycloalkenyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroaralkyl, and is optionally substituted with 1-3 J groups;

X is a bond, $-C(H)(R^7)-$, -O-, -S-, or $-N(R^8)-$;

R^7 is hydrogen, alkyl, alkenyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroaralkyl, and is optionally substitituted with 1-3 J groups;

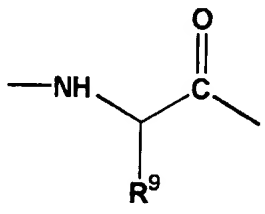
R^8 is hydrogen alkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, aralkanoyl, heterocyclanoyl, heteroaralkanoyl, $-C(O)R^{14}$, $-SO_2R^{14}$, or carboxamido, and is optionally substitituted with 1-3 J groups; or R^8 and Z, together with the atoms to which they are bound, form a nitrogen containing mono- or bicyclic ring system optionally substituted with 1-3 J groups;

R^{14} is alkyl, aryl, aralkyl, heterocyclyl, heterocyclyalkyl, heteroaryl, or heteroaralkyl;

Y is a bond, $-CH_2-$, $-C(O)-$, $-C(O)C(O)-$, $-S(O)-$, $-S(O)_2-$, or $-S(O)(NR^7)-$, wherein R^7 is as defined above;

Z is alkyl, aryl, aralkyl, cycloalkyl, cycloalkylalkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, $-OR^2$, or $-N(R^2)_2$, wherein any carbon atom is optionally substituted with J, wherein R^2 is as defined above;

A^2 is a bond or



;

R^9 is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, carboxyalkyl, or carboxamidoalkyl, and is optionally substituted with 1-3 J groups;

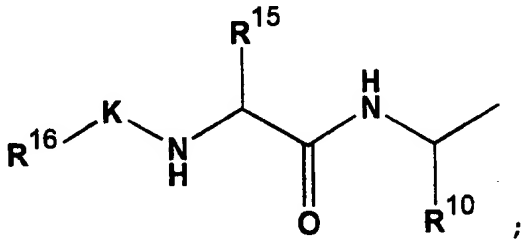
M is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, or heteroaralkyl, optionally substituted by 1-3 J groups, wherein any alkyl carbon atom may be replaced by a heteroatom;

V is a bond, $-CH_2-$, $-C(H)(R^{11})-$, $-O-$, $-S-$, or $-N(R^{11})-$;

R^{11} is hydrogen or C_{1-3} alkyl;

K is a bond, $-O-$, $-S-$, $-C(O)-$, $-S(O)-$, $-S(O)_2-$, or $-S(O)(NR^{11})-$, wherein R^{11} is as defined above;

T is $-R^{12}$, $-alkyl-R^{12}$, $-alkenyl-R^{12}$, $-alkynyl-R^{12}$, $-OR^{12}$, $-N(R^{12})_2$, $-C(O)R^{12}$, $-C(=NOalkyl)R^{12}$, or



;

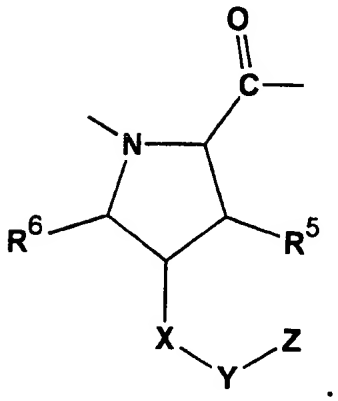
R^{12} is hydrogen, aryl, heteroaryl, cycloalkyl, heterocyclyl, cycloalkylidenyl, or heterocycloalkylidenyl, and is optionally substituted with 1-3 J groups, or a first R^{12} and a second R^{12}, together with the nitrogen to which they are bound, form a mono- or bicyclic ring system optionally substituted by 1-3 J groups;

R^{10} is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, carboxyalkyl, or carboxamidoalkyl, and is optionally substituted with 1-3 hydrogens J groups;

R^{15} is alkyl, cycloalkyl, aryl, aralkyl, heterocyclyl, heterocyclylalkyl, heteroaryl, heteroaralkyl, carboxyalkyl, or carboxamidoalkyl, and is optionally substituted with 1-3 J groups; and

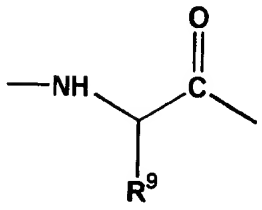
R^{16} is hydrogen, alkyl, aryl, heteroaryl, cycloalkyl, or heterocyclyl.

2. The compound according to claim 1, wherein A1 is:



3. The compound according to claim 2, wherein R^5 and R^6 are hydrogen.

4. The compound according to claim 3, wherein A^2 is:



and R^9 is alkyl.

5. The compound according to claim 4, wherein R^9 is isopropyl.

6. The compound according to claim 5, wherein L is alkyl, alkenyl, or alkynyl, wherein any hydrogen is optionally substituted with halogen, and wherein any hydrogen or halogen atom bound to any terminal carbon atom is optionally substituted with sulfhydryl or hydroxy.

7. The compound according to claim 6, wherein L is trihalomethyl, sulfhydryl, or alkyl substituted with trihalomethyl, sulfhydryl, or hydroxy.

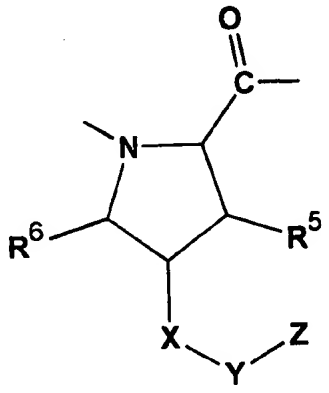
8. The compound according to claim 7, wherein:

X is -O- or -N(H)-; and

Y is $-CH_2-$, -C(O)-, or $-S(O)_2-$.

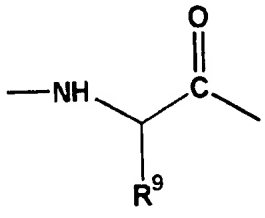
9. The compound according to claim 8, wherein V is -N(H)- and K is -C(O)- or $-S(O)_2-$.

10. The compound according to claim 1, wherein A^1 is:



, and R^5 and R^6 are hydrogen;

A^2 is:



and R^9 is isopropyl;

L is ethyl;

X is -O- or -N(H)-;

Y is $-CH_2-$, -C(O)-, or $-S(O)_2-$;

V is -N(H)-; and

K is -C(O)-.

11. The compound according to claim 10, wherein M is isopropyl.

12. The compound according to claim 11, wherein Z is aryl or heteroaryl.

13. The compound according to claim 12, wherein T is aryl or heteroaryl.

14. The compound according to claim 13, wherein T is pyrazine.

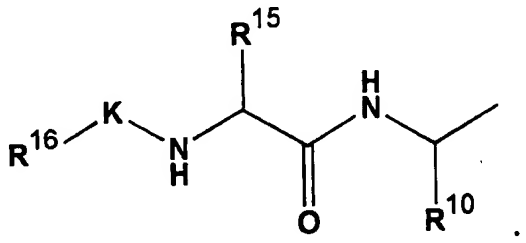
15. The compound according to claim 10, wherein X is -O- and Y is $-CH_2-$.

16. The compound according to claim 15, wherein Z is aryl or heteroaryl.

17. The compound according to claim 16, wherein Z is aryl.

18. The compound according to claim 10, wherein M is isopropyl.

19. The compound according to claim 18, wherein T is $-R^{12}$, $-OR^{12}$, $-N(R^{12})_2$, or



20. The compound according to claim 19, wherein M is alkyl, heteroaralkyl, aryl, cycloalkylalkyl, aralkyl, or aralkyl, wherein one of the alkyl carbon atoms is replaced by O or S.

21. The compound according to claim 20, wherein said heteroatom is S or O.

22. The compound according to claim 21, wherein T is aryl or heteroaryl.

23. The compound according to claim 22, wherein T is pyrazine.

24. The compound according to claim 3, wherein

A^2 is a bond;

L is ethyl;

X is -O-;

Y is $-CH_2-$;

V is -N(H)-; and

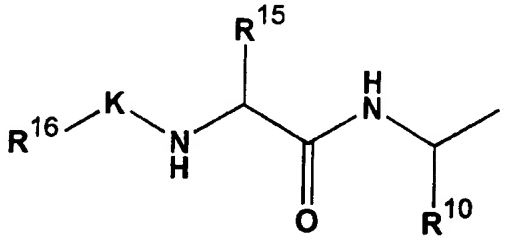
K is -C(O)- or $-S(O)_2-$.

25. The compound according to claim 24, wherein M is isopropyl.

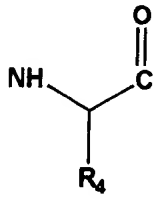
26. The compound according to claim 25, wherein Z is aryl or heteroaryl.

27. The compound according to claim 26, wherein Z is phenyl.

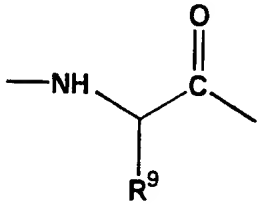
28. The compound according to claim 27, wherein T is $-R^{12}$, $-alkyl-R^{12}$, $-alkenyl-R^{12}$, $-OR^{12}$, $-N(R^{12})_2$, $-C(=NOalkyl)R^{12}$, or



29. The compound according to claim 1, wherein

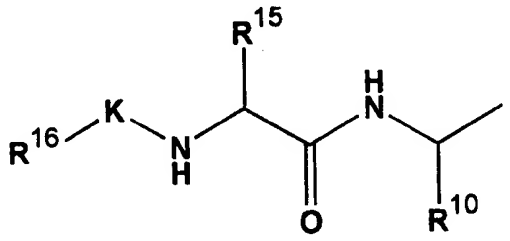
A^1 is  ; and

A^2 is

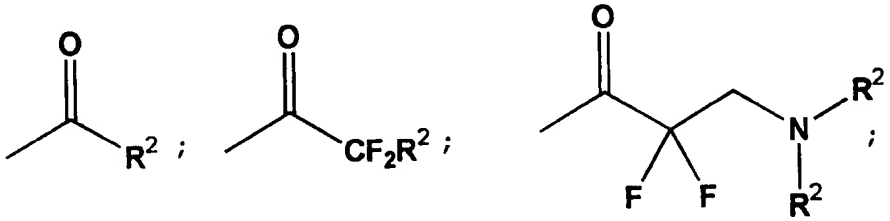


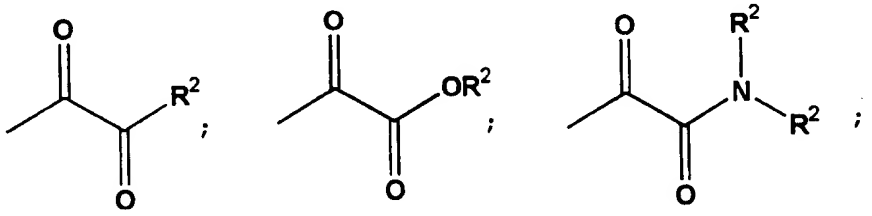
30. The compound according to claim 29, wherein M is isopropyl and K is -C(O)-.

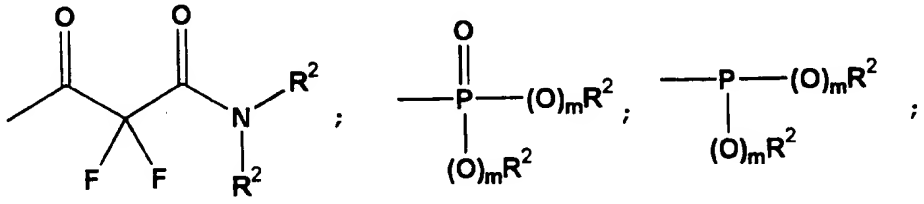
31. The compound according to claim 30, wherein T is $-R^{12}$, -alkyl-R^{12}, -alkenyl-R^{12}, $-OR^{12}$, $-N(R^{12})_2$, $-C(=NOalkyl)R^{12}$, or

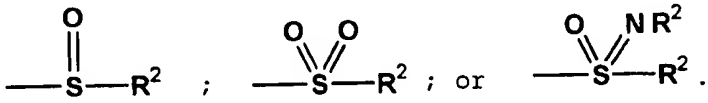


32. The compound according to any one of claims 1-31, wherein W is









33. A pharmaceutically acceptable composition comprising:

a) a compound according to claims 1-32 in an amount effective to inhibit HCV NS3 protease; and

b) a pharmaceutically suitable carrier.

34. A method for inhibiting serine protease activity comprising the step of administering to said patient a compound according to any one of claims 1-32.

35. The method according to claim 34, wherein the serine protease is HCV NS3 protease.

36. A method for treating or preventing a hepatitis C viral infection in a patient comprising the step of administering to said patient/mammal a compound according to any one of claims 1-32.

37. The method according to claim 36, wherein said compound is administered to a patient and is formulated together with a pharmaceutically suitable carrier into a pharmaceutically acceptable composition.

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/US 97/18968

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07K5/10 C07K7/06 C07K7/02 C07K5/02 A61K38/55

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07K A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 95 35308 A (VERTEX) 28 December 1995 see the whole document ---	1-37
A	WO 93 25574 A (PFIZER) 23 December 1993 see the whole document ---	1-37
X	EP 0 363 284 A (MERRELL DOW) 11 April 1990 see the whole document ---	1-37
X	EP 0 195 212 A (MERRELL DOW) 24 September 1986 see the whole document --- -/--	1-37

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
11 March 1998	26. 03. 1998

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Masturzo, P

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

Inte ional Application No
PCT/US 97/18968

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	S MEHDI ET AL.: "The inhibition of human neutrophil elastase and cathepsin C by peptidyl 1,2-dicarbonyl derivatives" BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS., vol. 166, no. 2, 30 January 1990, ORLANDO, FL US, pages 595-600, XP000085857 see the whole document ---	1-37

Form PCT/ISA/210 (continuation of second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 97/18968

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

see FURTHER INFORMATION sheet PCT/ISA/210

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Remark : Although claims 34-37 are directed to a method of treatment of the human/animal body , the search has been carried out and based on the alleged effects of the compound/composition.

INTERNATIONAL SEARCH REPORT

Information on patent family members

Int. Jonal Application No
PCT/US 97/18968

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INTERNATIONAL SEARCH REPORT

Information on patent family members

Inte ional Application No
PCT/US 97/18968

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		FI 94254 C	10-08-95
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